UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,096	11/19/2001	Anke Rattenholl	1406/415	2974

25297 7590 02/19/2008

JENKINS, WILSON, TAYLOR & HUNT, P. A.
3100 TOWER BLVD., Suite 1200
DURHAM, NC 27707

EXAMINER	
HAYES, ROBERT CLINTON	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
02/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/807,096	RATTENHOLL ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,20 and 26-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,20 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/11/07 has been entered.

2. Applicant's arguments filed 10/11/07 have been fully considered but they are not deemed to be persuasive.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 8, 10 & 26-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

No proper antecedent basis nor conception in context with that described within the specification at the time of filing the instant application exists for the recitation of “a

pharmaceutical preparation comprising… purified human proNGF… wherein… is purified *to at least about 90% purity and has an activity in vivo analogous to β-NGF*". In contrast to Applicants' assertions on page 7 of the response, page 16 of the specification refers to only inclusion bodies (IB) possessing a purity of "approx. 90-95% rh proNGF (Fig. 2)", which page 2 of the specification alternatively defines as "biologically ***inactive*** translation product[s]". Thus, such IBs cannot possess "an activity in vivo analogous to β-NGF", by definition. Nor can such IBs reasonably be contemplated as a "pharmaceutical preparation", which would require a biologically active proNGF molecule; thereby, constituting new matter for these new purity limitations.

Similarly, no proper antecedent basis nor conception in context with that described within the specification at the time of filing the instant application exists for the recitation of "an EC50 value… that is at least about 50% of that of human β-NGF on a molar basis". In contrast to Applicants' assertions on page 7 of the response, pages 22-23 of the specification contemplate "[c]onsidering the different molecular weight of rh β-NGF and rh proNGF, the biological activity of mature rh β-NGF [a]s about twice as high as that of rh proNGF", which is different in contemplation and scope from an EC50 value of 0.369 ng/ml versus 0.106 ng/ml" in a DRG assay, or "an EC50 value… that is at least about 50% of that of human β-NGF on a molar basis", as now claimed; thereby, also constituting new matter.

5. Claims 8, 20 & 26-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and incomplete for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "*at least about* 90%" (i.e., claim 8) or "*at least about* 50%" (claim 26) is indefinite because the limitation of "about" normally means 90 or 50 ± 5%, etc. while the limitation of "at least" removes any lower limit below 90% or 50%, respectively; thereby, being contradictory.

Second, the recitation of "activity in vivo analogous to β-NGF" is ambiguous because it is unknown what is considered an "analogous" activity when no such activity is defined in claim 8. It is suggested that amending claim 8 to "and promotes survival of DRG sensory neurons" should obviate this particular part of this rejection.

6. Claims 8, 20 & 26-28 are rejected under 35 U.S.C. 102(b) as anticipated by Edwards et al (U.S. Patent 5,683,894), and as described on page 4 of the specification where Edward's is acknowledged as admitted prior art for describing the "whole prosequence", and for the reasons made of record in Paper NOs: 20050124, 20050706, 20060329 & 20060913, and as follows.

The Lorey Declaration filed under 37 CFR 1.132 filed 10/11/07 is insufficient to overcome the rejection of the claims based upon the teaching of Edwards et al as set forth in the last Office action because: this declaration merely argues semantics regarding what is "purified" versus what is not "purified" as it relates to a single preferred example that "did not include an infection of the mouse L929 cells with a virus" (i.e., similar to Example 4, but ignoring the separate purification procedures disclosed in Examples 2 or 7, etc. by Edwards). Therefore, Declarant's opinion is not reasonably on point with what is accepted within the art, or MPEP 2111, which states that "the claims must be given their broadest reasonable interpretation consistent with the specification". In the instant case, the term "purified" is not defined in the

specification, and both the specification and Edwards use the same terminology of "purified", along with the term "recombinant" to refer to various degrees of "purified" proteins. In addition, Example 4 of Edwards actually states "[t]he lysates were cleared of particulate material by centrifugation… to provide a pro-NGF solution" (i.e., being further "purified", by definition). See also claim 1 of Edwards where proNGF is "so produced". Note that the terminology of a "pure homogenous protein" is not claimed, nor is it equivalent in scope to the relative terms of "purifying" or "purified", as further illustrated in amended claim 8, in which "purified" to only "about 90% purity" is now claimed. In other words, as previously made of record, the term "purified" or "substantially purified" are relative terms, in which no degree of purification to homogeneity is accepted within the art or alternatively described within the specification. Accordingly, as previously made of record, although Applicants are permitted to be their own lexicographer, no term may be given meaning repugnant to the usual meaning of the term (see MPEP 608.01 (o)), in regards to the breadth encompassed by any term; especially when the specification fails to specifically define the metes and bounds this term otherwise encompasses.

Applicants argue on pages 4-7 of the response that Edwards fails to teach substantially purified proNGF based on their current interpretation of the term "substantially purified", as argued in the Lorey Declaration, that "at best Edwards discloses a crude cellular lysate that includes murine proNGF", and that "Edwards disclose proNGF to have little or no activity... in the DRG assay (see Edwards at col. 9, lines 6-9)." In contrast to Applicants' assertions, the issue remains that Edward's anticipates the instant invention for the reasons discussed above, and below, in which only Example 4 is disclosed to "have little or no activity". Thus, Applicants' arguments related to their narrow interpretation of what Edwards actually teaches in his

"Example 4" is persuasive only as it relates to whether "murine" proNGF has at least 90% purity in Example 4 (i.e., as it relates to amended claim 8). However, note that MPEP 2123 states that "[t]he use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain", and that "[a] reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments".

In summary, Evans et al teach how to make a pharmaceutical composition comprising a recombinant pro-NGF-beta solution "derived from humans" (e.g., col. 4, lines 40-42), which inherently comprises SEQ ID NO: 4 and inherently is encoded by a nucleic acid comprising SEQ ID NO: 3 (i.e., as it relates to claims 20, 27 & 28). In that Example 2 (col. 7) teaches *in vitro* translated proNGF (i.e., including proNGF from "human, murine, bovine; col. 4, line 41), which therefore would reasonably be purified to least 90% purity based on this translation system, the limitations of claim 8 are anticipated; absent evidence to the contrary. In that proNGF produced by such a procedure inherently has whatever activity it possesses based on its structural characteristics, the limitations of claim 26 are also reasonably met.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8, 20 & 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gray & Ullrich (U.S. Patent 5,169,762) and Collins et al (U.S. Patent 5,235043).

Gray et al teach both the amino acid and nucleotide sequence of human proNGF (i.e., Figs. 4-6; as it relates to claims 27 & 28). Gray also teach methods of making NGF proteins recombinantly using either prokaryotic or eukaryotic host cells (e.g., cols. 3-6), as well as pharmaceutical compositions thereof (e.g., col. 13; as it relates to claims 8 & 20). Although Gray et al are silent regarding the activity of proNGF as it relates to β-NGF, the activity of proNGF is directly related to its structure, and therefore, is an inherent property of proNGF (i.e., as it relates to claim 26). However, Gray et al do not specifically teach pharmaceutical preparations of purified human proNGF protein of at least 90% purity.

Collins et al teach "production of purified forms of all members of the NGF/BDNF family of neurotrophic proteins which would be valuable as pharmaceutical preparations" (e.g., col. 5), as well as biologically active recombinant human NGF family member proteins (e.g., cols. 5, 9-10, & 24; Figs. 6 & 7; as it relates to claims 8, 20 & 27-28). Although Collins et al are silent regarding the activity of proNGF as it relates to β-NGF, the activity of proNGF is directly related to its structure, and therefore, is an inherent property of proNGF (i.e., as it relates to claim 26). Nevertheless, Collins et al teach that it was well accepted in the art that "the proper folding and assumption of biological activity of mature NGF will only occur if it is first synthesized as the full-length precursor, as occurs in eukaryotic cells and in natural sources" (i.e., col. 32, lines 62-65); thereby, providing motivation for making human proNGF protein nonetheless. However, Collins et al do not specifically teach pharmaceutical preparations of purified human proNGF protein of at least 90% purity.

It would have been obvious to one of ordinary skill in the art to make and purify human proNGF to homogeneity based on the teachings of both Gray and/or Collins using standard purification techniques known in the art, or as described by both Gray et al, or by Collins et al. , etc. either for use in pharmaceutical compositions, as suggested by Collins, in which the subsequent purification would reasonably minimize undesirable side effects and/or adverse immunological concerns well known in the art (thereby, increasing the number of neurotrophic proteins valuable for treating neurodegenerative diseases, as suggested by Collins (e.g., col. 5)), or for use of human proNGF as a prodrug for its eventual processing into a biologically active and mature NGF form, whose biological activity is well characterized within the art.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Stucker, can be reached on (571) 272-0911. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Robert C. Hayes, Ph.D./
Primary Examiner, Art Unit 1649
February 7, 2008